Synthesis and Nicotinic Acetylcholine Receptor Binding Properties of Bridged and Fused Ring Analogues of Epibatidine

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Epibatidine analogues **3**–**5**, possessing the pyridine ring fused to the 2,3 position of the 7-azabicyclo[2.2.1]heptane ring, and analogue **8a**, possessing a benzene ring fused to the 5,6 position, were synthesized by procedures involving key steps of trapping 2,3-pyridyne, 3,4-pyridyne, and benzyne with *tert*-butyl 1*H*-pyrrole-1-carboxylate. Two epibatidine analogues, **6** and **7**, which have the 2′-chloropyridine ring bridged to the 7-azabicyclo[2.2.1]heptane ring via a methylene group, were synthesized, where the key step was an intramolecular reductive palladium-catalyzed Heck-type coupling. Even though the conformationally restricted epibatidine analogues, **3**–**7**, and the benzo analogue **8a** possess nAChR pharmacophore features thought to be needed for $\alpha_4\beta_2$ binding, they all showed low affinity for nAChRs relative to epibatidine. These studies provide new information concerning the pharmacophore for nAChRs and suggest that nitrogen lone-pair directionality and steric factors may be important. Interestingly, *N*-methylepibatidine, prepared as a standard compound for the study of bridged analogues **6** and **7**, was a potent nAChR mixed agonist antagonist.

Introduction

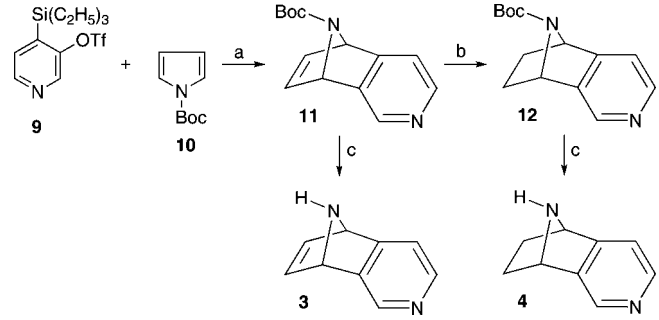
In 1992, Daly and co-workers reported the isolation and structure determination of a compound showing potent antinociceptive activity from the skin of the Ecuadorean poison frog, *Epipedobates tricolor*, which they named epibatidine.[1] Subsequent studies showed that the analgesic activity of epibatidine resulted from the interaction with nicotinic acetylcholine receptors (nAChRs).[a2–4] Epibatidine, similar to nicotine (**2**), possesses a pyridine ring connected to a second pyrrolidine ring. However, unlike nicotine, the pyrrolidine ring is less flexible because of the 2-carbon bridge between the 1 and 4 positions. In addition, the pyridine ring of epibatidine has a 2′-chloro substituent not present in nicotine. The unique structure and biological activity of epibatidine generated considerable interest and precipitated the synthesis and biological evaluation of a number of analogues as a means of learning more about the nAChR pharmacophore.[5–7] However, the exact conformation for receptor affinity and modulation is currently still in doubt.

To gain additional information on the nAChR pharmacophore, we synthesized and evaluated the nAChR binding affinity of the conformationally restricted epibatidine analogues **3**–**7**. In addition, because the 5,6-benzo analogue **8a** was reported to have high affinity for nAChR, we synthesized and evaluated the nAChR binding properties of this compound.[8] Preliminary results on the synthesis of **6** and **7** have been reported.[9]

Chemistry

The fused ring epibatidine analogues **3** and **4** were synthesized as outlined in Scheme 1. 3-Pyridyne, generated by treating 4-triethylsilylpyridin-3-yl trifluoromethanesulfonate (**9**)[10] with cesium fluoride in acetonitrile, was added to *tert*-butyl 1*H*-pyrrole-1-carboxylate (**10**) to give **11**. Catalytic hydrogenation of **11** using 10% palladium on carbon in ethyl acetate yielded **12**. Treatment of **11** and **12** with hydrogen chloride in methanol provided the desired 3,4-pyridine fused ring epibatidine analogues **3** and **4**, respectively. A totally different synthesis of **4**, which involved 16 steps and a very low overall yield, has been reported.[11]

Scheme 1[a]



[a] Reagents: (a) CsF, CH_3CN, 25 °C; (b) H_2, 10% Pd/C, EtOAc; (c) CH_3OH, HCl, 0 °C.

The 2,3-pyridine-ring-based analogue **5** was synthesized by a procedure similar to that for **4** (Scheme 2). 2-Pyridyne, generated by treating 3-trimethylsilylpyridin-2-yl trifluoromethanesulfonate (**13**)[12] with cesium fluoride in acetonitrile, was added to *tert*-butyl 1*H*-pyrrole-1-carboxylate (**10**) to give **14**. Catalytic reduction of **14** in ethyl acetate using 10% palladium on a carbon catalyst yielded **15**. Removal of the *tert*-butyloxycarbonyl protecting group using trifluoroacetic acid in methylene chloride provided **5**.

The bridged epibatidine analogue **6** was synthesized as shown in Scheme 3, starting with 2-amino-4-methylpyridine (**16**). Iodination of **16** using iodine in a periodic, sulfuric, and acetic acid mixture afforded a 71% yield of 2-amino-5-iodo-4-methylpyridine (**17**). The structure of **17** was established by analysis of the ^{1}H nuclear magnetic resonance (NMR) spectrum, which showed singlets at δ 2.23, 6.46, and 8.27 ppm for the C4-methyl, H-3, and H-6 protons, respectively. The reaction

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[a] Abbreviations: nAChR, nicotinic acetylcholine receptor; [^{3}H], tritium.

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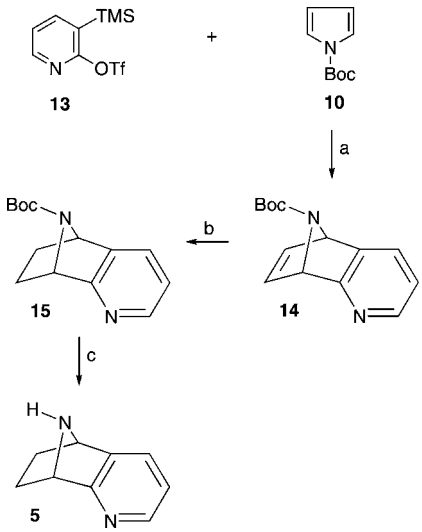
Scheme 2[a]



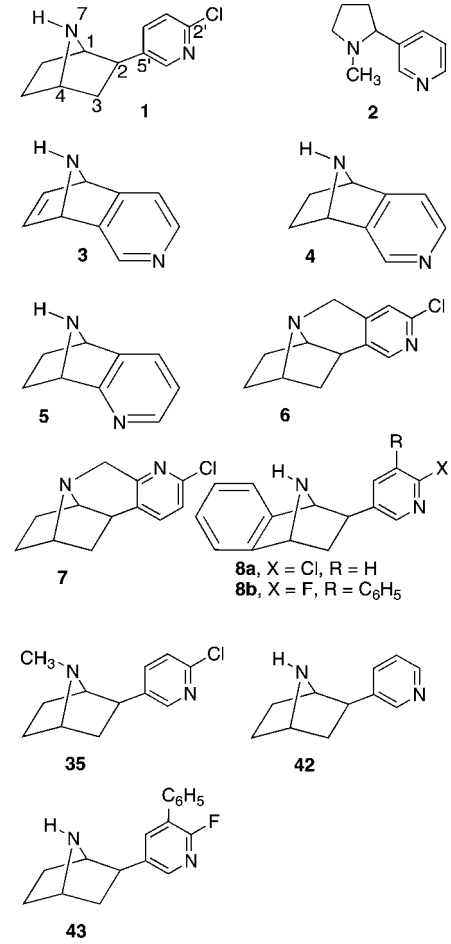
[a] Reagents: (a) CsF, CH_3CN, 25 °C; (b) H_2, 10% Pd/C, EtOAc; (c) TFA, CH_2Cl_2.

of **17** with *meta*-chloroperbenzoic acid in acetone gave the *N*-oxide **18**, which was isolated as the hydrochloride salt in 85% yield. Treatment of the hydrochloride salt of **18** with acetic anhydride in dioxane was expecting to give the 4-acetoxymethyl or 4-hydroxymethyl compounds **19a** and **19b**, respectively. Surprisingly, 2-acetamido-4-chloromethyl-5-iodopyridine (**19c**) was isolated in 56% yield. Apparently, chloride ion displaced the acetoxy or hydroxy group from the expected 4-acetoxymethyl or 4-hydroxymethyl intermediate to give **19c**. Alkylation of 7-azabicyclo[2.2.1]hept-2-ene (**20a**),[13] generated from *tert*-butoxycarbonyl-7-azabicyclo[2.2.1]hept-2-ene (**20b**) using trimethylsilyl iodide in chloroform, with **19c** provided the N-alkylated product **21** in 43% yield. Two possible approaches for the conversion of **21** to **22** were the Heck cyclization[14–16] and a radical initiated cyclization.[17,18] We found that intramolecular cyclization of **21** using reductive Heck conditions similar to that used for intermolecular coupling[19] (palladium diacetate, potassium formate, and tetrabutyl ammonium chloride in dimethylformamide at 90 °C) provided the hexahydro-7,10-methanopyrrolo-2-[1,2-*b*]-2,6-naphthyridine **22** in 45% yield. Hydrolysis of **22** using refluxing 3 N hydrochloric acid gave a 90% yield of the 3-amino analogue **23**. Diazotization of **23** using sodium nitrite in concentrated hydrochloric acid yielded the desired epibatidine analogue **6** in 28% yield.

Bridged epibatidine analogue **7** was synthesized from 2-amino-6-methylpyridine (**24**) by a set of reactions exactly analogous to those used to prepare analogue **6** that proceeded through intermediate **24**−**30** (see Figure 1). The yield in each step was similar to the analogous step in the synthesis of **6**.

4′-Methylepibatidine (**32**), 6′-methylepibatidine (**34**), and *N*-methylepibatidine (**35**) were synthesized as reference compounds for a comparison to the nAChR binding affinities of the bridged analogues **6** and **7**. The synthesis of compounds **32** and **34** is shown in Scheme 4. Subjection of **20b** to reductive Heck[19] conditions using 2-amino-5-iodo-4-methylpyridine (**36a**) or 2-amino-5-iodo-6-methylpyridine (**36b**) provided the intermediates **31** and **33**. Diazotization of **31** and **33** using sodium nitrite and concentrated hydrochloric acid yielded the desired 4′-methyl- and 6′-methylepibatidine analogues **32** and **34**, respectively. *N*-Methylepibatidine (**35**) was prepared as previously reported.[20]

The 5,6-benzofused ring epibatidine analogues **8a** and **8b** were synthesized as outlined in Scheme 5. Benzyne, generated by treating 2-trimethylsilyl trifluoromethanesulfonate (**37**)[21–23] with cesium fluoride in acetonitrile, was added to *tert*-butyl 1*H*-pyrrole-1-carboxylate (**10**) to give **38**. Subjection of **38** to reductive Heck conditions using 2-amino-5-iodopyridine gave **39**. Diazotization of **39** using sodium nitrite in concentrated hydrochloride acid yielded the desired **8a**. Bromination of **39** provided **40**. The palladium-acetate-catalyzed reaction of **40** with phenylboronic acid in dimethoxyethane in the presence of tri-(2-tolyl)phosphine and sodium carbonate gave the *tert*-butoxycarbonyl-protected 2-amino-3-phenyl analogue **41**. Diazotization of **41** using sodium nitrite in pyridine containing 70% hydrogen fluoride yielded the desired 2-fluoro-3-phenyl analogue **8b**.



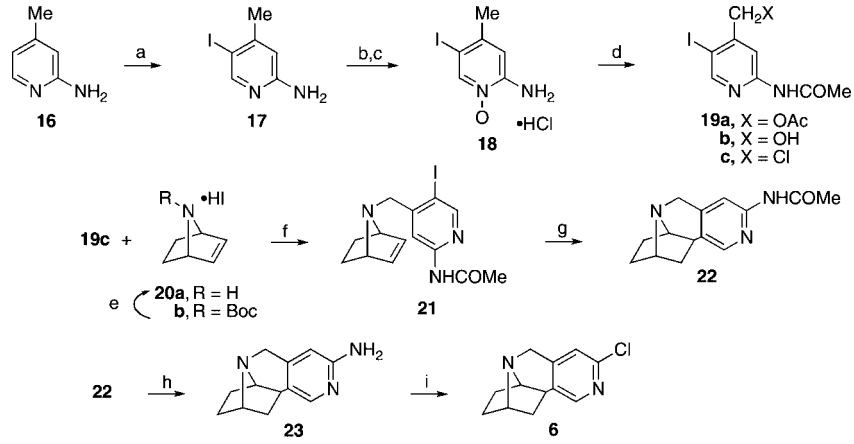
Biology

The inhibition of [^{3}H]epibatidine binding at $\alpha4\beta2$ nAChRs and [^{125}I]iodo-MLA at α_7 nAChRs, respectively, were conducted as previously reported.[24] The epibatidine analogues were tested for their effects on body temperature and two pain models after acute administration as previously described.[24] For the antagonist experiments, mice were pretreated s.c. with either saline or epibatidine analogues 10 min before nicotine. Nicotine was administered at a dose of 2.5 mg/kg, s.c. (an ED_{84} dose), and mice were tested 5 min later. ED_{50} and AD_{50} values with 95% confidence limits were determined.

Results and Discussion

The key steps in the synthesis of the pyridine ring fused epibatidine analogues **3–5** and **8a–8b** were the trapping of 2,3-pyridyne, 2,4-pyridyne, and benzyne with *tert*-butyl 1-pyrrole-

Scheme 3[a]



[a] Reagents: (a) H_5IO_6, I2, H_2SO_4, HOAc, H_2O, 80 °C; (b) MCPBA; (c) ethereal HCl; (d) Ac_2O, dioxane; (e) $(CH_3)_3SiI$, $CHCl_3$; (f) NaOMe, MeOH; (g) HCO_2K, $Pd(OAc)_2$, $(C_4H_9)_4N^+Cl^-$, DMF, 90 °C; (h) 3 N HCl, reflux; (i) $NaNO_2$, concentrated HCl.

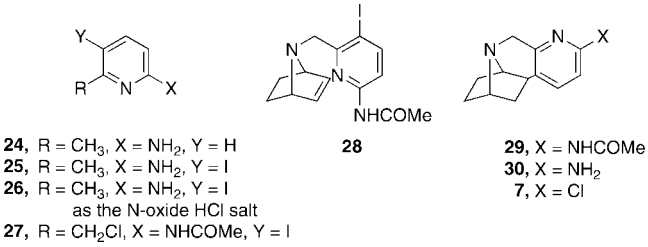
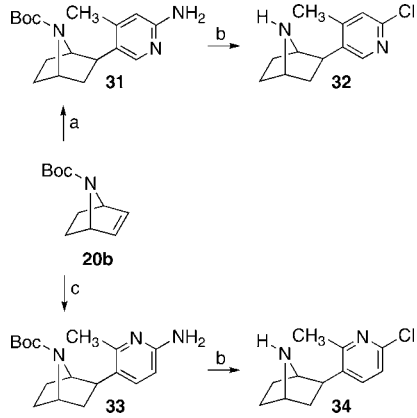


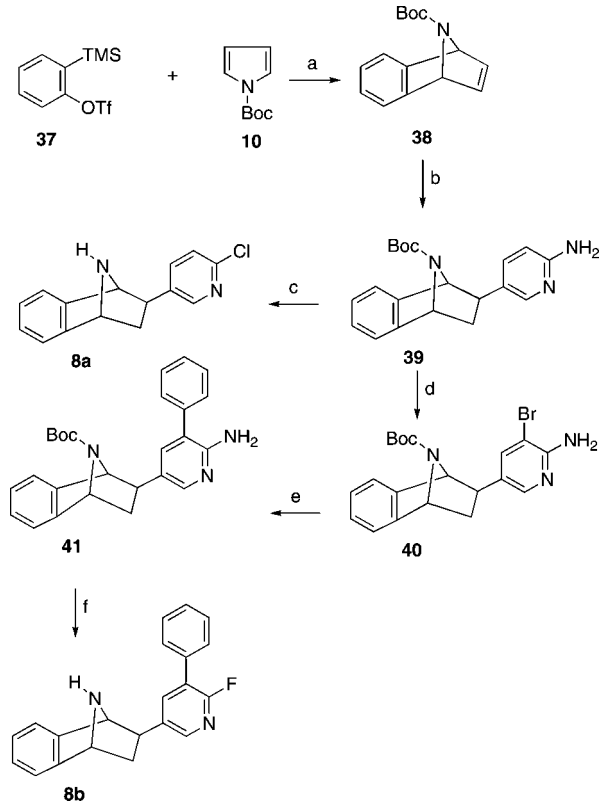
Figure 1. Structures of starting material and intermediates used to synthesize **7**.

Scheme 4[a]



[a] Reagents: (a) 2-amino-5-iodo-4-methylpyridine (**36a**), HCO_2K, $Pd(OAc)_2$, $(C_4H_9)_4N^+Cl^-$, DMF, 120 °C; (b) $NaNO_2$, concentrated HCl; (c) 2-amino-5-iodo-6-methylpyridine (**36b**), HCO_2K, $Pd(OAc)_2$, $(C_4H_9)_4N^+Cl^-$, DMF, 100 °C.

Scheme 5[a]



[a] Reagents: (a) CsF, CH_3CN; (b) 2-amino-5-iodopyridine, $HCO_2^-K^+$, $(C_4H_9)_4N^+Cl^-$, $Pd(Cl_2)_2$, DMF, 60 °C; c) Na_2NO_2, concentrated HCl; (d) Br_2, $(C_2H_5)_3N$, HOAc; (e) $C_6H_5B(OH)_2$, $P(o\text{-tolyl})_3$, DME, H_2O, 90 °C; (f) pyridine, HF, $NaNO_2$.

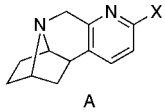
1-carboxalate to give intermediate compounds **11**, **14**, and **38** that could be modified using standard chemical techniques to provide the desired target compounds. The key steps in the synthesis of the bridged epibatidine analogues **6** and **7** were intramolecular reductive Heck cyclization of **21**−**22** and **28**−**29**.

The inhibition of radioligand binding for the 2,3- and 3,4-pyridine fused ring epibatidine analogues **3**–**5** and the 5,6-benzene fused analogues **8a**–**8b** is given in Table 1. The pyridine-fused analogues **3**–**5** displace less than 15% of the radioligand at 31.6 μM for $\alpha_4\beta_2$ nAChRs and have no affinity for α_7 nAChRs (Table 1). Geometrically, the fused analogues **3** and **4** are quite different from epibatidine. The fixed nitrogen−nitrogen distance in the rigid analogues **3** and **4** (4.56 Å) is near the low end of the range of corresponding distances found in the conformations of epibatidine (4.58−5.66 Å). The torsional angle (as measured between the azabicylo ring bridgehead atoms and the pyridinyl ring) is also different: for the fused analogues, this torsional angle is ∼0°, whereas the corresponding angle is either 70° or 256° for the two minimum-energy conformations of epibatidine. One could speculate that this is due to the fact that analogues **3**–**5** do not possess a chloro substituent comparable to the 2′-chloro group in epibatidine. However, this seems unlikely because deschloroepibatidine (**42**) has a $K_i = 0.02$ nM for the $\alpha_4\beta_2$ nAChR.[25] It seems much more likely that these conformationally rigid analogues do not possess features required for the $\alpha_4\beta_2$ or α_7 nAChR pharmacophores.

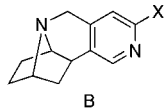
Table 1. Radioligand Binding Data for Benzene- and Pyridine-Fused Epibatidine Analogues

compound	X	Y	$\alpha_4\beta_2$ [^{3}H]epibatidine (K_i, nM) or percent inhibition	α_7 [^{125}I]iodoMLA percent inhibition
nicotine (**2**)			1.50 ± 0.30	
epibatidine (**1**)			0.026 ± 0.002	
3			<15% at 31.6 μM	0% at 50 nM
4			<15% at 31.6 μM	0% at 50 nM
5			<15% at 31.6 μM	0% at 50 nM
8a			65.2 ± 7.2	0% at 50 nM
8b			128 ± 22	0% at 50 nM

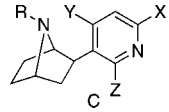
Table 2. Radioligand Binding Data for Bridged Ring Epibatidine Analogues



A



B



C

compound	structure	X	Y	Z	R	$\alpha_4\beta_2$ [^{3}H]epibatidine (K_i, nM)
(+)-epibatidine	C	Cl	H	H	H	0.026 ± 0.002
6	B	Cl				3330 ± 310
7	A	Cl				1260 ± 400
23	B	NH_2				12400 ± 900
30	A	NH_2				7370 ± 1240
32	C	Cl	CH_3	H	H	17.2 ± 2.2
34	C	Cl	H	CH_3	H	256 ± 74
35	C	Cl	H	H	CH_3	0.038 ± 0.003[a]

[a] Ref 20 reports a K_i = 0.027 nM.

Even so, the information from the study of these compounds does help further define nAChR pharmacophores.

The 5,6-benzo fused epibatidine analogue **8a** has a K_i = 65.2 nM at the $\alpha_4\beta_2$ nAChR and has no affinity for the α_7 nAChR. The most likely explanation for the low binding affinity of **8a** compared to epibatidine is that the nAChRs cannot accommodate the extra steric bulk added to the 5,6 position. In earlier studies, we showed that 2′-fluoro-3′-phenyldeschloroepibatidine (**43**) had a K_i = 0.24 nM at the $\alpha_4\beta_2$ nAChR. The 5,6-benzo analogue **8b** has a K_i = 128 nM,[26] again showing that steric bulk is not allowed in the 5,6 position.

The bridged epibatidine analogues **6** and **7** have K_i values of 3330 and 1260 nM, respectively, for the $\alpha_4\beta_2$ nAChR (Table 2). Compounds **6** and **7** can be viewed as conformationally locked analogues of epibatidine and are comparable to the two principal low-energy conformations of the freely rotating pyridine ring in epibatidine.[27–30] It has been suggested that the pharmacologically significant conformation of epibatidine is the global energy minimum conformation.[31–33] In the "syn" conformation of epibatidine, the N−C1−C2−N dihedral angle is ∼42°, while in compound **7**, the corresponding dihedral angle is ∼43°.[34] In the "anti" conformation of epibatidine, the N−C1−C2−N dihedral angle is ∼133°, while in compound **6**, the corresponding dihedral angle is ∼138°. The nitrogen−nitrogen distances are somewhat shorter in the bridged analogues than in the corresponding epibatidine conformations (3.8 versus 4.6 Å for compound **7**/"syn" epibatidine pair and 5.1 versus 5.6 Å for compound **6**/"anti" epibatidine pair). However, the nitrogen−nitrogen distance for compound **6** in particular is within the 4.5−5.5 Å range that has been proposed by several authors for the nicotinic pharmacophore.[27–30]

Thus, even though the analogues **6** and/or **7** possess several of the structural features in proposed pharmacophores for the $\alpha_4\beta_2$ nAChR, they did not show high affinity for this receptor site. To determine if the bridged ring epibatidine analogues **6**, **7**, **23**, or **30** might be allosteric modulators of the nAChR system, the compounds were evaluated for their in vivo nicotinic pharmacological properties in mice (Table 3). Consistent with the lack of affinity for the $\alpha_4\beta_2$ receptor, the compounds possessed no antinociceptive activity in the tail-flick or hot-plate tests or significantly changed body temperature.

One could speculate that the reason for the low binding affinity of the bridged analogues **6** and **7** is that they have an extra 4′- and 6′-methylene substituents not present in epibatidine. Alternatively, compounds **6** and **7** could be viewed as N-substituted analogues of epibatidine. To gain information on this possible explanation, we synthesized and evaluated the $\alpha_4\beta_2$ nAChR binding affinity of the 4′-methyl-, 6′-methyl-, and *N*-methylepibatidine analogues **32**, **34**, and **35**, respectively. The 4′-methyl and 6-methyl analogues have K_i values of 17.2 and 256 nM, respectively (Table 2). Thus, it seems unlikely that the extra methylene substituents in **6** and **7** play a major part in their low $\alpha_4\beta_2$ nAChR affinity. Because *N*-methylepibatidine has a K_i = 0.038 nM at the $\alpha_4\beta_2$ nAChR, apparently N substitution does not contribute to the low affinity of the bridged analogues **6** and **7**. Compounds **32**, **34**, and **35** were also evaluated for their in vivo nicotinic pharmacological properties (Table 3). Compound **35** has an ED_{50} = 0.004 mg/kg in the tail-flick test, which is consistent with the previously reported value of 0.009 mg/kg.[35] It also had an ED_{50} of 0.003 mg/kg in both the hot-plate and hypothermia tests. Surprisingly, *N*-methylepibatidine also blocked nicotine-induced antinociception in the tail-flick test with a very high potency (AD_{50} = 0.048 μg/kg), which is 90 times greater than its agonist activity. Compounds **32** and **34** blocked the analgesic effects of nicotine in the tail-flick test with a potency that correlates with their affinity in the [^{3}H]epibatidine binding assay. Only compound **32** blocked nicotinic effects in the hot-plate test.

In summary, methods were developed for the synthesis of three epibatidine analogues (**3**–**5**), which have the pyridine ring annotated to the 3,4 position of the 7-azabicyclo[2.2.1]heptane ring, and two analogues (**6** and **7**), which have a 2′-chloropyridine ring bridged to the 7 position of the 7-azabicyclo[2.2.1]-heptane ring via a methylene group. Similar to previously reported conformationally restricted epibatidine analogues,[36,37] compounds **3**–**7** possessed low affinity for the nAChR relative to that for epibatidine and did not show any activity in the nicotinic pharmacological test in mice. Nevertheless, results from this study provide valuable information concerning the pharmacophore for nAChRs. In addition, we developed a new synthesis of an epibatidine analogue (**8a**) possessing a benzene ring fused to the 5,6 position on the 7-azabicyclo[2.2.1]heptane ring. We found that **8a** possessed low affinity for nAChRs, which is in contrast to a reported value.[8] Results from this study show that these structures do not encompass the ideal conformation for high affinity to the nAChRs. The fact that the nitrogen−nitrogen distance in the analogues are within the range generally required for receptor recognition suggests that directionality of the nitrogen lone pair of epibatidine's 7-amino group or steric hindrance may explain their lack of nAChR binding affinity. Surprisingly, *N*-methyepibatidine is a potent mixed agonist/antagonist.

Experimental Section

Melting points were determined on a Mel-temp (Laboratory Devices, Inc.) capillary tube apparatus. NMR spectra were recorded on a Bruker Avance 300 or AMSX 500 spectrometer using tetramethylsilane as an internal standard. Thin-layer chromatography was carried out on Whatman silica gel 60 plates. Visualization was accomplished under UV or in an iodine chamber. Microanalysis was carried out by Atlantic Microlab, Inc. Flash chromatography

Table 3. Pharmacological Data for Epibatidine Analogues

compound	ED_{50} mg/kg tail flick	ED_{50} mg/kg hot plate	ED_{50} mg/kg hypothermia	AD_{50} (μg/kg) tail flick	AD_{50} (μg/kg) hot plate	AD_{50} (μg/kg) body temperature
1	0.006	0.004	0.004			
6	2% at 10	18% at 10	0% at 10			
7	3% at 10	17% at 10	0% at 10			
23	2% at 10	16% at 10	0% at 10			
30	4% at 10	10% at 10	0% at 10			
32	4% at 10	20% at 10	0% at 10	400 (300–600)	1200 (1000–1800)	0% at 5000
34	1% at 10	14% at 10	0% at 10	9000 (8600–9600)	10% at 15 000	0% at 15 000
35	0.0044 (0.002–0.006)	0.003 (0.001–0.004)	0.003 (0.002–0.006)	0.048 (0.01–0.17)	23% at 0.5	0% at 0.5

was carried out using silica gel 60 (230–400 mesh). CMA80 is 80% $CHCl_3$−18% CH_3OH−2% NH_4OH.

The [^{3}H]epibatidine was purchased from Perkin-Elmer Inc. (Boston, MA). The [^{125}I]iodo-MLA was synthesized as previously reported.[38]

4-(Triethylsilyl)pyridin-3-yl Trifluoromethanesulfonate (9). The title compound was synthesized by a modification of the reported method.[10] Diethylcarbamoyl chloride (74.9 mL, 552 mmol) was added to a stirred, cold (0 °C) solution of 3-hydroxypyridine (50.0 g, 0.526 mol) in 263 mL of pyridine. The solution warmed to room temperature overnight. Water was added, and the mixture was extracted with ether. The combine ether extracts were washed with 10% aqueous sodium carbonate solution and brine, dried with magnesium sulfate, filtered, and evaporated to yield 92.3 g (90%) of pyridin-3-yl diethylcarbamate as a yellow oil. ^{1}H NMR ($CDCl_3$) δ: 8.44 (dd, J = 1.5, 4.8 Hz, 2H), 7.53 (m, 1H), 7.30 (m, 1H), 3.46 (q, J = 7.2 Hz, 2H), 3.40 (q, J = 7.2 Hz, 2H), 1.27 (t, J = 7.2 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ: 153.5, 148.2, 146.2, 143.6, 129.3, 123.6, 42.4, 42.0, 14.2, 13.3.

Lithium diisopropylamide [85.0 mL, 170 mmol, 2 M solution in tetrahydrofuran (THF)] was added dropwise over 15 min to a cold (−78 °C) solution of 30.0 g (0.154 mol) of the compound above in 309 mL of THF. The reaction mixture was stirred for 25 min, at which time chlorotriethylsilane (170 mL, 170 mmol, 1 M solution in THF) was added dropwise over 15 min. The solution was allowed to warm to room temperature overnight. Water was added, and the mixture was extracted with ether. The combined ether extracts were washed with brine, dried with magnesium sulfate, filtered, and evaporated. Flash chromatography over silica gel with 50% ethyl acetate in hexanes provided 42.7 g (90%) of 4-(triethylsilyl)pyridin-3-yl diethylcarbamate as a clear crystalline solid. ^{1}H NMR ($CDCl_3$) δ: 8.39 (d, J = 4.5 Hz, 1H), 8.33 (s, 1H), 7.33 (d, J = 4.8 Hz, 1H), 3.49 (q, J = 7.2 Hz, 2H), 3.40 (q, J = 7.2 Hz, 2H), 1.27 (t, J = 7.2 Hz, 3H), 1.20 (t, J = 7.2 Hz, 3H), 0.95 (m, 9H), 0.85 (m, 6H). ^{13}C NMR ($CDCl_3$) δ: 154.0, 153.1, 145.3, 144.3, 138.8, 129.7, 42.2, 41.8, 14.3, 13.3, 7.4, 3.2.

Methanol (50 mL) was added to a solution of 40.1 g (0.130 mol) of the above compound in 300 mL of 25% sodium methoxide in methanol. The solution was stirred at room temperature overnight. Hydrochloric acid (10%) was added dropwise, and the mixture was extracted with ether. The combined ether extracts were washed with brine, dried with magnesium sulfate, filtered, and evaporated. Flash chromatography over silica gel with 50% ethyl acetate in hexanes provided 21.6 g (80%) of 4-triethylsilyl)pyridin-3-ol as a white solid. ^{1}H NMR ($CDCl_3$) δ: 11.8 (s, 1H), 8.26 (s, 1H), 8.02 (d, J = 3 Hz, 1H), 7.30 (d, J = 3 Hz, 1H), 0.96 (m, 15H). ^{13}C NMR ($CDCl_3$) δ: 160.5, 138.6, 135.5, 135.4, 131.2, 7.8, 3.3.

Trifluoromethanesu1fonic anhydride (18.8 mL, 112 mmol) was added dropwise over 10 min to a cooled (0 °C), stirred solution of 21.3 g (0.102 mol) of the above compound in 102 mL of pyridine. The reaction mixture was allowed to warm to room temperature overnight. Water was added, and the mixture was extracted with ether. The combined ether extracts were washed with brine, dried with magnesium sulfate, filtered, and evaporated. Flash chromatography over silica gel with 10% ethyl acetate in hexanes provided 23.5 g (68%) of **9** as a clear, colorless oil. ^{1}H NMR ($CDCl_3$) δ: 8.61 (s, 1H), 8.56 (d, J = 4.5 Hz, 1H), 7.42 (d, J = 4.8 Hz, 1H), 0.95 (m, 15H). ^{13}NMR ($CDCl_3$) δ: 152.6, 148.3, 141.5, 140.7, 131.3, 119.0 (d, J = 320 Hz), 7.8, 3.3.

***tert*-Butyl 5,8-Dihydro-5,8-epiminoisoquinoline-9-carboxylate (11).** Anhydrous cesium fluoride (20.9 g, 0.138 mol) was added to a stirred solution of 4-triethylsilylpyridin-3-yl trifluoromethanesulfonate (**9**, 23.5 g, 0.07 mol) and *t*-butyl 1-pyrrole-1-carboxylate (**10**, 57.5 g, 0.344 mol) in 69 mL of anhydrous acetonitrile. The solution was allowed to stir overnight at room temperature. Water was added, and the mixture was extracted with ether. The combined ether extracts were washed with brine, dried with magnesium sulfate, filtered, and evaporated. Flash chromatography over silica gel with 50% hexanes in ethyl acetate afforded 6.3 g of an orange oi1. Distillation of the oil at 95–100 °C (0.067 torr) provided 4.72 g (28%) of **11** as a white solid. ^{1}H NMR ($CDCl_3$) δ: 8.46 (s, 1H), 8.29 (d, J = 4.5 Hz, 1H), 7.25 (s, 1H), 7.00 (s, 1H), 6.95 (s, 1H), 5.58 (s, 1H), 5.52 (s, 1H) 1.38 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 158.1, 154.7, 147.5, 143.8, 142.9, 142.0, 140.4, 116.7, 81.2, 65.9, 64.6, 28.1.

5,8-Dihydro-5,8-iminoisoquinoline (3). Ice-cold concentrated hydrochloric acid (10 mL) was added to a stirred solution of **11** (400 mg, l.64 mmol) in 2.0 mL of methanol cooled to 0 °C. The reaction mixture was stirred at 0 °C for 3 h. Concentrated ammonium hydroxide (15 mL) was added dropwise, and the product was extracted with chloroform. The chloroform extracts were combined, dried with sodium sulfate, and evaporated. Flash chromatography over silica gel with 5% methanol in ethyl acetate provided 165 mg (70%) of **3** as a clear, colorless oil. ^{1}H NMR ($CDCl_3$) δ: 8.42 (s, 1H), 8.23 (d, J = 4.5 Hz, 1H), 7.22 (d, J = 4.5 Hz, 1H), 7.05 (5, 1H), 6.98 (5, 1H), 5.08 (s, 1H), 5.01 (s, 1H), 3.11 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ: 147.0, 145.3, 143.7, 140.3, 116.6, 66.0, 64.4 ppm. Anal. Calcd ($C_9H_8N_2$): C, H, N.

***tert*-Butyl 5,6,7,8-Tetrahydro-5,8-epiminoisoquinoline-9-carboxylate (12).** Compound **11** (500 mg, 2.05 mmol) was weighed in a Parr vessel and diluted with 35 mL of ethyl acetate. Palladium (10%) on carbon (100 mg) was added, and the solution was hydrogenated at 30 psi for 14 h. The catalyst was removed by filtration over celite, and the ethyl acetate was evaporated to yield 410 mg (81%) of **12** as a white solid. ^{1}H NMR ($CDCl_3$) δ: 8.45 (s, 1H), 8.38 (d, J = 4.5 Hz, 1H), 7.22 (d, J = 4.5 Hz, 1H), 5.20 (s, 1H), 5.14 (s, 1H), 2.18 (m, 2H), 1.39 (s, 9H), 1.27 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 155.4, 153.8, 148.8, 140.9, 140.6, 115.5, 81.0, 61.0, 59.6, 28.5, 26.8, 26.2.

5,6,7,8-Tetrahydro-5,8-iminoisoquinoline (4). Ice-cold concentrated hydrochloric acid (3 mL) was added to a stirred, 0 °C solution of **12** (190 mg, 0.771 mmol) in 2.0 mL of methanol. The reaction mixture was stirred at 0 °C for 1 h. Concentrated ammonium hydroxide (5 mL) was added dropwise, and the product was extracted with chloroform. The chloroform extracts were combined, dried with sodium sulfate, filtered, and evaporated. Flash chromatography over silica gel with 50% methanol in ethyl acetate provided 60.0 mg (53%) of a clear, colorless oil. ^{1}H NMR ($CDCl_3$) δ: 8.44 (s, 1H), 8.36 (d, J = 3 Hz, 1H), 7.18 (d, J = 4.5 Hz, 1H), 4.64 (d, J = 4.5 Hz, 1H), 4.58 (d, J = 3 Hz, 1H), 2.60 (br s, 1H), 2.08 (m, 2H), 1.27 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 157.4, 148.2, 144.1, 140.4, 115.3, 61.0, 59.3, 26.5, 26.0. To a stirred, 0 °C solution of the free amine (60.0 mg, 0.410 mmol) in methylene chloride was added hydrochloric acid in ether (1.0 mL, 1.01 mmol, 1 M). The solution was stirred for 2 h while warming to room tempera-

ture. The solution was evaporated, and the resulting solid was dried on the vacuum pump. Recrystallization from methanol−ether provided 62 mg (73%) of **4**·HCl as small, white needles. Anal. Calcd ($C_9H_{12}C1_2N_2$): C, H, N.

3-Trimethylsilyl-2-pyridyl Trifluoromethanesulfonate (13). The title compound was prepared by modification of the reported method.[12] Lithium diisopropylamide (2 M, 231 mL, 463 mmol) was added dropwise over 15 min to a stirred, 0 °C solution of 20.0 g (0.210 mol) of 2-hydroxypyridine in 500 mL of THF under nitrogen. The solution was stirred for 5 min at 0 °C and for 1 h while warming to room temperature. The solution was again placed in an ice bath, and chlorotrimethylsilane (29.3 mL, 231 mmol) was added over 10 min to the solution. After stirring 5 min longer at 0 °C, the solution was allowed to stir overnight at room temperature. The THF was evaporated, and ethyl acetate was added. The ethyl acetate was filtered and evaporated. Flash chromatography over silica gel with ethyl acetate yielded 23.4 g (67%) of 3-trimethylsilyl-2-hydroxypyridine as an off-white solid. ^{1}H NMR ($CDCl_3$) δ: 12.4 (br s, 1H), 7.54 (d, J = 6 Hz, 1H), 7.34 (d, J = 6 Hz, 1H), 6.23 (t, J = 6 Hz, 1H), 0.28 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 167.7, 147.5, 135.5, 132.1, 106.7, −1.6.

To a stirred, ice-cold solution of 3-trimethylsilyl-2-hydroxypyridine (5.56 g, 0.033 mol) in 33 mL of pyridine under nitrogen was added dropwise trifluoromethanesulfonic anhydride (6.15 mL, 36.6 mmol). The solution was allowed to stir at room temperature overnight. The solvent was evaporated, and ether and water were added. The ether extracts were washed with brine, dried with magnesium sulfate, filtered, and evaporated. Flash chromatography over silica gel with 5% ethyl acetate in hexanes provided 9.50 g (96%) of **13** as a clear, colorless oi1. ^{1}H NMR ($CDCl_3$) δ: 8.32 (dd, J = 1.8, 4.8 Hz, 1H), 7.92 (dd, J = 1.8, 7.2 Hz, 1H), 7.31 (dd, J = 4.8, 7.2 Hz, 1H), 0.37 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 161.1, 149.0, 147.1, 125.4, 123.4, 120.8, 118.7 (d, J_{cf} = 317 Hz), −1.4.

***tert*-Butyl 5,8-Dihydro-5,8-epiminoquinoline-9-carboxylate (14).** Cesium fluoride (30.0 g, 0.198 mol) was added to a stirred solution of **13** (29.6 g, 0.099 mol) and *tert*-butyl 1-pyrrolecarboxylate (82.6 g, 0.494 mol) in 100 mL of acetonitrile at room temperature. The reaction was allowed to stir overnight. Water was added, and the reaction mixture was extracted with ethyl acetate. The ethyl acetate fractions were combined, washed with brine, dried with magnesium sulfate, filtered, and evaporated. Flash chromatography over silica gel with 20% ethyl acetate in hexanes provided 6.6 g of a bright yellow solid. Distillation at 90 °C (0.054 torr) provided 3.4 g (14%) of **14** a white solid. ^{1}H NMR ($CDCl_3$) δ: 8.02 (d, J = 5.4 Hz, 1H), 7.42 (d, J = 7.2 Hz, 1H), 7.04 (br s, 2H), 6.84 (dd, J = 5.4, 7.2, 1H), 5.56 (s, 1H), 5.43 (s, 1H), 1.40 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 171.5, 154.9, 143.6, 141.6, 126.9, 119.3, 81.2, 67.6, 65.4, 28.1.

This product was used in the next step without further purification.

***tert*-Butyl 5,6,7,8-Tetrahydro-5,8-epiminoquinoline-9-carboxylate (15).** Compound **14** (476 mg, 1.95 mmol) was weighed in a Parr vessel and diluted with 35 mL of ethyl acetate. Palladium (10%) on carbon (100 mg) was added, and the solution was hydrogenated at 30 psi for 15 h. The catalyst was removed by filtration over celite, and the ethyl acetate was evaporated to yield 434 mg (91%) of **14** as a white solid. ^{1}H NMR ($CDCl_3$) δ: 8.27 (dd, J = 1.5, 5.1 Hz, 1H), 7.44 (d, J = 7.5 Hz, 1H), 7.04 (dd, J = 5.1, 7.2 Hz, 1H), 5.18 (d, J = 2.7 Hz, 1H), 5.13 (d, J = 3.9, 1H), 2.18 (m, 2H), 1.41 (s, 9H), 1.27 (m, 2H).

This product was used in the next step without further purification.

3,11-Diazatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene (5) Dihydrochloride. Trifluoroacetic acid (2 mL) was added to a stirred, –9 °C solution of **15** (450 mg, 1.83 mmol) in 2.0 mL of methylene chloride. The reaction mixture was stirred at 0 °C for 30 min and 2 h while warming to room temperature. Concentrated ammonium hydroxide (3 mL) was added dropwise, and the product was extracted with methylene chloride. The methylene chloride extracts were combined, washed with brine, dried with sodium sulfate, filtered, and evaporated. Flash chromatography over silica gel with 50% methanol in ethyl acetate provided 160 mg (60%) of **5** as a clear, colorless oil. ^{1}H NMR ($CDCl_3$) δ: 8.20 (dd, J = 1.5, 5.1 Hz, 1H), 7.44 (d, J = 7.5 Hz, 1H), 6.97 (dd, J = 5.1, 7.2 Hz, 1H), 4.60 (d, J = 2.7 Hz, 1H), 4.52 (d, J = 3.9, 1H), 2.4 (br s, 1H), 2.12 (m, 2H), 1.35 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 169.6, 146.4, 141.6, 126.8, 121.2, 62.1, 60.4, 26.9, 25.2. To a stirred, 0 °C solution of the free amine (21.5 mg, 0.147 mmol) in methylene chloride was added hydrochloric acid in ether (1.5 mL, 1.47 mmol, 1 M). The solution was evaporated, and the resulting solid was dried on the vacuum pump. Recrystallization from methanol−ether provided 31.4 mg (98%) of the dihydrochloride salt. mp 175.5 °C (decomp). Anal. Calcd ($C_9H_{12}Cl_2N_2$): C, H, N.

2-Amino-5-iodo-4-methylpyridine (17). Compound **16** (27.0 g, 0.25 mol) was mixed with periodic acid (11.4 g, 0.050 mol), HOAc (150 mL), H_2SO_4 (4.5 mL), and H_2O (30 mL). Iodine (25.4 g, 0.10 mol) was added, and the reaction mixture was stirred at 80 °C for 4 h. The mixture was cooled and poured into H_2O containing 40 g of $Na_2S_2O_3$. The reaction mixture was decanted from a reddish oil, and the filtrate was basified with 50% NaOH. The resulting solids were extracted with diethyl ether (2 × 300 mL). The ether layer was separated, dried (Na_2SO_4), and concentrated. The solids were recrystallized from EtOH−H_2O to afford **17** (41.8 g, 71%) as a tan solid. ^{1}H NMR ($CDCl_3$) δ: 2.23 (s, 3H), 4.35 (br s, 2H), 6.46 (s, 1H), 8.27 (s, 1H).

2-Amino-5-iodo-4-methylpyridine-*N*-oxide (18) Hydrochloride. To compound **17** (29.6 g, 0.13 mol) in acetone (200 mL) was added *meta*-chloroperbenzoic acid (50–55%, 48.3 g) in acetone (100 mL). The reaction was stirred at room temperature for 90 min and then concentrated in vacuo. The residue was dissolved in $CHCl_3$ and stirred while adding 2 M ethereal HCl (100 mL). The mixture was filtered, and the salt was recrystallized from EtOH−diethyl ether to yield **18** hydrochloride (30.8 g, 85%) as a tan solid. mp 198–200 °C. ^{1}H NMR (DMSO-d_6) δ: 2.34 (s, 3H), 7.08 (s, 1H), 8.39 (br s, 3H), 8.74 (s, H).

2-Acetamido-4-chloromethyl-5-iodopyridine (19c). Acetic anhydride (2.4 g, 0.023 mol) was added to a heterogeneous mixture of **18**·HCl (3.0 g, 0.0105 mol) in dioxane (50 mL). The reaction mixture was stirred at reflux for 17 h. The resulting dark brown mixture was concentrated in vacuo, and the residue was partitioned between 5% $NaHCO_3$ solution and CH_2Cl_2. The organic layer was separated, washed with brine, dried (Na_2SO_4), and concentrated. The residue was dissolved in EtOAc and passed through a plug of silica gel. The filtrate was concentrated to give 2.9 g of a tan solid. The resulting product was purified by flash chromatography on silica gel using 75% hexane−acetone, as the eluent, to yield **19c** (1.82 g, 56%) as a beige solid. mp 173–174 °C. ^{1}H NMR ($CDCl_3$) δ: 2.22 (s, 3H), 4.57 (s, 2H), 7.98 (br s, 1H), 8.37 (s, 1H), 8.50 (s, 1H).

7-Azabicyclo[2.2.1]hept-2-ene (20a). Iodotrimethylsilane (4.84 g, 0.024 mol) was added to a solution of 7-(*tert*-butoxy)carbonyl-7-azabicyclo[2.2.1]hept-2-ene[1] (**20b**, 3.9 g, 0.02 mol) in 150 mL of $CHCl_3$. The reaction mixture was stirred at room temperature for 1 h, quenched with MeOH (3.1 g, 0.097 mol), and concentrated. The residue was triturated with ether to give **20a** (3.26 g, 73%) as a tan solid. mp 184–185 °C. ^{1}H NMR ($CDCl_3$) δ: 1.45 (dd, J = 3.6, 8.7 Hz, 2H), 2.42 (m, 2H), 4.90 (s, 2H), 6.40 (s, 2H), 7.95 (br s, 1H).

***N*-[4-(7-Azabicyclo[2.2.1]hept-2-en-7-yl)methyl-5-iodo-2-pyridin-2-yl] Acetamide (21).** To NaOMe (0.26 g, 0.0045 mol) in MeOH (50 mL) was added **20a** (1.0 g, 0.0045 mol) followed by **19c** (1.29 g, 0.0044 mol). The reaction mixture was stirred at reflux for 18 h then concentrated in vacuo. The solid residue was triturated with $CHCl_3$, filtered, and concentrated. The solids were purified by silica gel column chromatography using EtOAc−hexane (1:1) as the eluent to give **21** (0.50 g, 43%) as a beige solid. mp 130–132 °C. ^{1}H NMR ($CDCl_3$) δ: 1.03 (m, 2H), 1.93 (d, J = 7.8 Hz, 2H), 2.20 (s, 3H), 3.34 (s, 2H), 3.88 (s, 2H), 6.05 (s, 2H), 8.00 (s, 1H), 8.34 (s, 1H), 8.44 (s, 1H).

This product was used in the next step without further purification.

***N*-(5,7,8,9,9a,10-Hexahydro-7,10-methanopyrrolo[1,2-*b*][2,6]naphthyridin-3-yl)acetamide (22).** To *N*,*N*-dimethylformamide (DMF, 10 mL) in a closed reaction vessel was added

compound **21** (1.60 g, 0.0043 mol), HCO_2K (0.36 g, 0.0043 mol), tetrabutylammonium chloride (0.31 g, 0.0043 mol), and palladium (II) acetate (0.047 g, 0.000 21 mol). The reaction mixture was stirred at 90 °C for 19 h and cooled, and brine (100 mL) and EtOAc (100 mL) were added followed by NH_4OH (50 mL). The mixture was filtered, and the organic layer was separated, washed with brine, dried (Na_2SO_4), and concentrated to give solids. The solids were purified by silica gel column chromatography using CMA80−hexane−EtOAc (2:1:1) as the eluent to afford **22** (0.45 g, 45%) as a beige solid. mp 204–205 °C. ^{1}H NMR ($CDCl_3$) δ: 1.34 (m, 1H), 1.48 (m, 2H), 1.88 (m, 3H), 2.18 (s, 3H), 2.87 (d, J = 6.5 Hz, 1H), 3.09 (d, 1H), 3.48 (t, J = 4.3 Hz, 1H), 3.95 (d, J = 19 Hz, 1H), 4.38 (d, J = 19 Hz, 1H), 7.92 (s, 11H), 7.99 (s, 1H), 8.45 (br s, 1H).

5,7,8,9,9a,10-Hexahydro-7,10-methanopyrrolo[1,2-*b*][2,6]naphthyridin-3-amine (23). Compound **22** (1.10 g, 0.0045 mol) was stirred at reflux in 3 N HCl (400 mL) for 7 h. The reaction was cooled, basified with solid NaOH, and extracted with $CHCl_3$ (2 × 200 mL). The combined $CHCl_3$ extracts were washed with brine, separated, and dried (Na_2SO_4). Evaporation of the solvent gave **23** (0.82 g, 90%) as a cream-colored solid. mp 149–152 °C. The hydrochloride salt obtained by adding an ethereal HCl solution to a solution of the free base in CH_2Cl_2 had an mp of 283–286 °C. ^{1}H NMR (base, $CDCl_3$) δ: 1.46–1.88 (m, 6H), 2.81 (d, J = 6.0 Hz, 1H), 3.07 (d, J = 5.0 Hz, 1H), 3.44 (t, J = 4.5 Hz, 1H), 3.84 (d, J = 19 Hz, 1H), 4.23 (d, J = 19 Hz, 1H), 4.29 (br s, 2H), 6.24 (s, 1H), 7.68 (s, 1H). Anal. Calcd (di-HCl salt) ($C_{12}H_{17}Cl_2N_3 \cdot H_2O$): C, H, N.

3-Chloro-5,7,8,9,9a,10-hexahydro-7,10-methanopyrrolo[1,2-*b*][2,6]naphthyridine (6). $NaNO_2$ (3.1 g, 0.045 mol) was added to compound **23** (0.65 g, 0.0032 mol) in 12 N HCl (20 mL) at ice bath temperatures, and the mixture was stirred for 30 min and then at room temperature for 2 h. The mixture was added to NH_4OH (40 mL), extracted with $CHCl_3$ (2 × 100 mL), separated, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using CMA80−hexane−EtOAc (2:1:1) as the eluent to afford **6** (0.20 g, 28%) as a beige solid. mp 138–139 °C. ^{1}H NMR ($CDCl_3$) δ: 1.34–1.95 (m, 6H), 2.92 (d, J = 6 Hz, 1H), 3.08 (d, J = 5 Hz, 1H), 3.49 (t, J = 5 Hz, 1H), 3.98 (d, J = 19 Hz, 1H), 4.31 (d, J = 19 Hz, 1H), 7.04 (s, 1H), 8.00 (s, 1H). Anal. Calcd ($C_{12}H_{13}ClN_2$): C, H, N.

2-Amino-5-iodo-6-methylpyridine (25). Compound **25** was prepared from 2-amino-6-methylpyridine **23** by a procedure similar to that used for **17** to afford 49% of **25** as a beige solid. mp 100–102 °C. ^{1}H NMR ($CDCl_3$) δ: 2.54 (s, 3H), 4.54 (br s, 2H), 6.17 (d, J = 8 Hz, 1H), 7.66 (d, J = 8 Hz, 1H).

This product was used in the next step without further purification.

2-Amino-5-iodo-6-methylpyridine-N-oxide (26) Hydrochloride. The title compound was prepared from **25** following the same procedure used for **18** to yield **26**, as a copper-colored solid. ^{1}H NMR (CD_3OH) δ: 2.54 (s, 3H), 4.95 (bs, 3H), 6.22 (d, J = 7.7 Hz, 1H), 7.68 (d, J = 7.8 Hz, 1H).

2-Acetamido-6-chloromethyl-5-iodopyridine (27). Using a procedure analogous to that described for **19c**, an overall 82% yield of **27** from **26** was obtained as a tan solid. mp 146–149 °C. ^{1}H NMR ($CDCl_3$) δ: 2.21 (s, 3H), 4.71 (s, 2H), 7.91 (br s, H), 7.94 (s, 1H), 8.04 (d, J = 8 Hz, 1H).

***N*-[6-(7-Azabicyclo[2.2.1]hept-2-en-7-yl)methyl-5-iodopyridin-2-yl] Acetamide (28).** Using a procedure analogous to that described for **21** gave an 81% yield of **28** as a beige solid. mp 128–130 °C. ^{1}H NMR ($CDCl_3$) δ: 0.96 (d, J = 7 Hz, 2H), 1.82 (d, J = 8 Hz, 2H), 2.10 (s, 3H), 3.55 (s, 2H), 3.91 (s, 2H), 6.04 (s, 2H), 7.82 (d, J = 8.4 Hz, 1H), 7.98 (d, J = 8.6 Hz, 1H), 8.84 (br s, 1H).

***N*-(5,5a,6,7,8,10-hexahydro-5,8-methanopyrrolo[2,1-*g*][1,7]naphthyridin-2-yl)acetamine (29).** Using a procedure analogous to that described for **22** gave a 43% yield of **29** as a tan solid. mp 129–132 °C. ^{1}H NMR ($CDCl_3$) δ: 1.33 (m, 1H), 1.51 (m, 2H), 1.88 (m, 3H), 2.16 (s, 3H), 2.86 (d, J = 6.5 Hz, 1H), 3.18 (d, 1H), 3.53 (t, J = 4.3 Hz, 1H), 3.89 (d, J = 19 Hz, 1H), 4.28 (d, J = 19 Hz, 1H), 7.24 (d, J = 8 Hz, 1H), 7.87 (d, J = 8 Hz, 1H), 8.61 (br s, 1H).

5,5a,6,7,8,10-Hexahydro-5,8-methanopyrrolo[2,1-*g*][1,7]napthyridin-2-amine (30). Using a procedure analogous to that described for **23** afforded a 61% yield of **30** as a white solid. mp (HCl salt) 201–206 °C. ^{1}H NMR (base, $CDCl_3$) δ: 1.29–1.86 (m, 6H), 2.73 (d, J = 6 Hz, 1H), 3.16 (d, J = 5 Hz, 1H), 3.49 (t, J = 5 Hz, 1H), 3.85 (d, J = 19 Hz, 1H), 4.26 (d, J = 19 Hz, 1H), 4.29 (br s, 2H), 6.21 (d, J = 8 Hz, 1H), 7.01 (d, J = 8 Hz, 1H).

2-Chloro-5,5a,6,7,8,10-hexahydro-5,8-methanopyrrolo[2,1-*g*][1,7]naphthyridine (7). Using a procedure analogous to that described for **6** gave a 32% yield of **7** as a white solid. mp 127–129 °C. ^{1}H NMR ($CDCl_3$) δ: 1.33–1.89 (m, 6H), 2.88 (d, J = 6 Hz, 1H), 3.17 (d, J = 5 Hz, 1H), 3.54 (t, J = 5 Hz, 1H), 3.98 (d, J = 19 Hz, 1H), 4.41 (d, J = 19 Hz, 1H), 7.04 (d, J = 8 Hz, 1H), 7.21 (d, J = 8 Hz, 1H). Anal. Calcd ($C_{12}H_{13}ClN_2 \cdot 0.25H_2O$): C, H, N.

***tert*-Butyl 2-(6-Amino-4-methylpyridin-3-yl)-7-azabicyclo-[2.2.1]heptane-7-carboxylate (31).** To DMF (10 mL) in a closed reaction vessel was added 2-amino-5-iodo-4-methylpyridine (**36a**, 3.60 g, 0.015 mol), compound **20b** (1.5 g, 0.0077 mol), HCO_2K (1.30 g, 0.015 mol), tetrabutylammonium chloride (0.53 g, 0.0019 mol), and palladium (II) acetate (0.094 g, 0.000 42 mol). The reaction was stirred at 120 °C for 17 h and cooled, and EtOAc (200 mL) was added followed by NH_4OH (200 mL). The organic layer was separated, washed with brine, dried (Na_2SO_4), and concentrated to give **31** as a solid. The solid was purified by silica gel column chromatography using 80% EtOAc−MeOH as the eluent to yield 0.25 g (11%) of **31** as a tan solid. ^{1}H NMR ($CDCl_3$) δ: 1.44 (s, 9H), 1.56 (t, J = 9.0 Hz, 2H), 1.65–1.95 (m, 5H), 2.16 (s, 3H), 2.86 (m, 1H), 4.23 (bd, 2H), 4.35 (bs, 1H), 6.33 (s, H), 8.04 (s, 1H).

2-(6-Chloro-4-methylpyridin-3-yl)-7-azabicyclo[2.2.1]heptane (32). $NaNO_2$ (5.3 g, 0.077 mol) was added to compound **31** (1.30 g, 0.0043 mol) in 12 N HCl (14 mL) at ice bath temperatures. The reaction mixture was stirred at ice bath temperatures for 30 min and then at room temperature for 2 h. The mixture was added to NH_4OH (75 mL) and extracted with $CHCl_3$ (2 × 100 mL). The $CHCl_3$ layer was separated, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using CMA80−hexane−EtOAc (2:1:1) as the eluent to afford 0.35 g (40%) of **32** as an orange oil. The HCl salt was prepared by dissolving the free base in ether and adding ethereal HCl to give solids that were crystallized from MeOH−EtOAc mixtures to yield the hydrochloride as a white solid. mp 120–122 °C. ^{1}H NMR ($CDCl_3$, free base) δ: 1.51–1.69 (m, 6H), 1.92 (m, 1H), 2.87 (m, 1H), 3.70 (m, 1H), 3.81 (m, 1H), 7.02 (s, 1H), 8.39 (s, 1H). Anal. Calcd ($C_{12}H_{16}Cl_2N_2 \cdot 1.25H_2O$): C, H, N.

***tert*-Butyl 2-(6-Amino-2-methylpyridin-3-yl)-7-azabicyclo-[2.2.1]heptane-7-carboxylate (33).** 2-Amino-5-iodo-6-methylpyridine (**36b**, 4.79 g, 0.021 mol), HCO_2K (1.72 g, 0.021 mol), and $Bu_4N^+Cl^-$ (709 mg, 2.55 mmol), fol1owed by DMF (10 mL), was added to a reaction tube containing **20b** (2.00 g, 10.2 mmol) in DMF (10 mL). $Pd(OAc)_2$ (114 mg, 0.51 mmol) was added to the reaction mixture. The mixture was placed under a N_2 atmosphere, sealed, and heated at 100 °C in an oil bath for 24 h. The reaction mixture was cooled to room temperature and diluted with EtOAc (100 mL). NH_4OH (15%, 100 mL) was added to the reaction mixture, and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 50 mL). The organic layer was collected and dried (Na_2SO_4), and the solvent was removed under reduced pressure to give a solid that was purified by column chromatography using CMA80−EtOAc−hexanes (2:1:1) as the eluent to afford 1.48 g (47%) of **33** as a yellow oil.

6′-Methylepibatidine (34) Hydrochloride. Concentrated HCl (20 mL, 37%), cooled to 0 °C, was added to **33** (900 mg, 2.97 mmol) at 0 °C and stirred for 45 min. At 0 °C, $NaNO_2$ (4.10 mg, 5.94 mmol) was added in small portions and the reaction mixture was stirred at 0 °C for an additional 30 min. The reaction mixture was warmed to room temperature and stirred for 1 h. The mixture was poured into ice (75 g) containing NH_4OH (30%, 75 mL) and extracted with $CHCl_3$

(8 × 50 mL). The organic layer was collected and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The resulting solid was purified by column chromatography using CMA80−EtOAc−hexanes (2:1:1) as the solvent mixture to afford 0.207 g (31%) of **34** as a clear, colorless oil. ^{1}H NMR ($CDCl_3$) δ: 7.78 (d, J = 8.2 Hz, 1H), 7.09 (d, J = 8.3 Hz, 1H), 3.78 (t, J = 4.0 Hz, 1H), 3.62 (m, 1H), 2.86 (dd, J = 5.1, 8.9 Hz, 1H), 2.49 (s, 3H), 1.92 (dd, J = 12.0, 9.0 Hz, 1H), 1.62 (m, 6H). ^{13}C NMR ($CDCl_3$) δ: 157.2, 147.4, 139.1, 136.7, 121.8, 61.7, 56.9, 42.9, 39.6, 31.7, 30.7, 22.7. LRMS (ES) m/z: 223.2 $(M + H)^+$. A sample was converted to the hydrochloride salt. Anal. Calcd ($C_{12}H_{16}Cl_2N_2 \cdot 0.75H_2O$): C, H, N.

***N*-Methylepibatidine (35) Hydrochloride.** Epibatidine (0.70 g, 0.00335 mol), paraformaldehyde (3.5 g, 0.167 mol), and formic acid (20 mL) were placed in a sealed vessel and stirred at 110 °C for 5 h. The flask was cooled, diluted with water (200 mL), basified with 50% NaOH, and extracted with CH_2Cl_2 (200 mL). The organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo to afford 0.30 g of a beige solid. The base was dissolved in ether (75 mL), filtered, and acidified with ethereal HCl. The mixture was concentrated by a stream of nitrogen gas and then dried in a vacuum oven to afford 0.23 g (24%) of **35** as a white solid. mp 180–184 °C. ^{1}H NMR ($CDCl_3$) δ: 1.68–1.95 (m, 6H), 2.26 (s, 3H), 2.57–2.62 (dd, J = 5, 9 Hz, 1H), 3.17 (br s, 1H), 3.34 (br s, 1H), 8.22 (s, 1H), 8.48 (s, 1H), 8.65 (s, 1H). Anal. Calcd ($C_{12}H_{16}Cl_2N_2 \cdot 1^2/_3H_2O$): C, H, N.

***tert*-Butyl 1,4-Dihydro-1,4-epiminonaphthalene-9-carboxylate (38).** 2-Trimethylsilylphenyl trifluoromethanesulfonate (**37**, 2.98 g, 0.010 mol) was stirred overnight at room temperature with *t*-butyl 1-pyrrolecarboxylate (**10**, 1.67 g, 0.010 mol) and anhydrous cesium fluoride (1.67 g, 0.011 mol) in 10 mL of anhydrous acetonitrile. The solid was filtered, and the solvent was evaporated. Ether was added, and a solid formed that was separated. The ether was evaporated to yield a yellow oil. Flash chromatography over silica gel with 20% ethyl acetate in hexane afforded 1.21 g (50%) of **38** as a white solid. ^{1}H NMR ($CDCl_3$) δ: 7.25 (s, 2H), 6.96 (m, 4H), 5.48 (s, 2H), 1.37 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 155.5, 148.7, 143.9, 142.8, 125.3, 121.4, 121.1, 80.9, 67.2, 66.6, 28.5.

This product was used in the next step without further purification.

***tert*-Butyl 2-(6-Aminopyridin-3-yl)-1,2,3,4-tetrahydro-1,4-epiminonaphthalene-9-carboxylate (39).** A solution of **38** (1.00 g, 0.004 mol), 2-amino-5-iodopyridlne (1.08 g, 0.005 mol), potassium formate (691 mg, 8.22 mmol), tetrabutyl ammonium chloride (286 mg, 1.03 mmol), and palladium (II) chloride (152 mg) in 8.2 mL of DMF was stirred for 18 h at 60 °C under nitrogen. Water was added, and the mixture was extracted with ethyl acetate. The combined ethyl acetate extracts were washed with brine, dried with magnesium sulfate, filtered, and evaporated. Flash chromatography over silica gel with 5% methanol in ethyl acetate afforded 500 mg (36%) of **39** as a white solid. ^{1}H NMR ($CDCl_3$) δ: 7.98 (s, 1H), 7.55 (d, J = 8.1 Hz, 1H), 7.29 (s, 2H), 7.16 (m, 2H), 6.50 (d, J = 8.4 Hz, 1H), 5.23 (s, 1H), 4.95 (s, 1H), 4.42 (br s, 2H), 2.73 (dd, J = 4.2,8.4, 1H), 2.10 (dt, J = 4.5, 11.7 Hz, 1H), 1.89 (d, J = 9, 11.7, 1H) 1.32 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 157.5, 147.3, 146.0, 137.0, 130.0, 126.8; 126.7, 120.2, 109.0, 80.5, 67.8, 61.5, 43.2, 37.7, 28.4.

This product was used in the next step without further purification.

2-(6-Chloropyridin-3-yl)-1,2,3,4-tetrahydro-1,4-epiminonaphthalene (8a). To a stirred, 0 °C solution of **39** (200 mg, 0.593 mmol) in 2.0 mL of concentrated hydrochloric acid was slowly added sodium nitrite (736 mg, 10.7 mmol). The reaction mixture was stirred for 1 h at 0 °C. A solution of 50% ammonium hydroxide in water was added dropwise to the solution, and the solution was extracted with chloroform. The combined chloroform extracts were washed with brine, dried with magnesium sulfate, filtered, and evaporated. Flash chromatography over silica gel with 50% methanol in ethyl acetate afforded 40.0 mg (26%) of **8a** as a light yellow oil. ^{1}H NMR ($CDCl_3$) δ: 8.37 (d, J = 2.4 Hz, 1H), 7.98 (dd, J = 2.4, 8.4 Hz, 1H), 7.20 (m, 4H), 4.66 (d, J = 3.9 Hz, 1H), 4.37 (s, 1H), 2.76 (dd, J = 4.5, 8.4 Hz, 1H), 2.35 (br s, 1H), 1.99 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 149.8, 149.6, 149.1, 140.5, 138.4, 126.6, 126.4, 124.2, 119.9, 119.6, 67.7, 61.5, 42.2, 37.9. The free amine was dissolved in 3 mL of ether at 0 °C. Hydrochloric acid in ether (0.13 mL, 0.136 mmol, 1 M) was added. The solution was stirred for 1 h, and the ether was evaporated to yield 45 mg (100%) of a white solid (hydrochloride salt). mp 186 °C (decomp). Anal. Calcd ($C_{15}H_{14}Cl_2N_2 \cdot {}^2/_3H_2O$): C, H, N.

***tert*-Butyl 2-(6-Amino-5-bromopyridin-3-yl)-1,2,3,4-tetrahydro-1,4-epiminonaphthalene-9-carboxylate (40).** Bromine (0.24 mL, 4.67 mmol) and triethylamine (0.24 mL) were added, under nitrogen, dropwise to a stirred, 0 °C solution of **39** (1.05 g, 0.003 mol) in 7.0 mL of acetic acid and 7.8 mL of methylene chloride. After stirring at 0 °C for 4 h, the solution was neutralized with 50% ammonium hydroxide in water and extracted with chloroform. The combined chloroform extracts were dried with magnesium sulfate, filtered, and evaporated. Flash chromatography of the residue over silica gel with 20% ethyl acetate in hexane afforded 810 mg (62%) of **40** as a white solid. ^{1}H NMR ($CDCl_3$) δ: 7.94 (s, 1H), 7.78 (s, 1H), 7.30 (m, 2H), 7.15 (m, 2H), 5.24 (br s, 1H), 5.00 (br s, 2H), 4.95 (s, 1H), 2.72 (dd, J = 4.5, 8.7, 1H), 2.07 (dt, J = 4.5, 11.7, 1H), 1.90 (dd, J = 8.7, 12 Hz, 1H), 1.34 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 155.8, 154.7, 146.4, 146.1, 139.5, 131.8, 127.1, 126.9, 120.4, 120.1, 105.1, 80.8, 67.8, 61.6, 42.9, 38.0, 28.6.

This product was used in the next step without further purification.

***tert*-Butyl 2-(6-Amino-5-phenylpyridin-3-yl)-1,2,3,4-tetrahydro-1,4-epiminonaphthalene-9-carboxylate (41).** A solution of **40** (500 mg, 0.0012 mol), sodium carbonate (255 mg, 2.40 mmol), phenylboronic acid (234 mg, 1.92 mmol), tri(*o*-tolyl)phosphine (7.3 mg, 0.024 mmol), palladium (II) acetate (2.7 mg, 0.012 mmol), and 0.9 mL degassed water in 4.8 mL of dimethyl ethylene glycol was placed in a sealed tube, stirred, and heated at 90 °C for 22 h. Saturated sodium bicarbonate solution was added, and the solution was extracted with ethyl acetate. The combined ethyl acetate extracts were washed with brine, dried with magnesium sulfate, filtered, and evaporated. Flash chromatography over silica gel with 50% ethyl acetate in hexane afforded 468 mg (94%) of **41** as a white solid. ^{1}H NMR ($CDCl_3$) δ: 8.00 (d, J = 2.4 Hz, 1H), 7.49 (d, J = 2.4 Hz, 1H), 7.38 (m, 7H), 7.16 (dd, J = 3, 5.4 Hz, 2H), 5.24 (br s, 1H), 5.01 (s, 1H), 4.59 (br s, 2H), 2.78 (dd, J = 4.5, 8.7, 1H), 2.15 (dt, J = 4.5, 11.7, 1H), 1.91 (dd, J = 8.7, 12 Hz, 1H), 1.29 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 155.6, 155.1, 146.5, 146.3, 138.6, 137.3, 130.7, 129.4, 129.1, 128.2, 127.0, 126.9, 122.3, 120.4, 120.1, 80.6, 67.9, 61.5, 43.3, 37.9, 28.6.

This product was used in the next step without further purification.

2-(6-Fluoro-5-phenylpyridin-3-yl)-1,2,3,4-tetrahydro-1,4-epiminonaphthalene (8b). To a stirred, –9 °C solution of **41** (232 mg, 0.561 mmol) in 1.0 mL of anhydrous pyridine was added dropwise 2.0 mL of hydrofluoric acid in pyridine (7:3). Sodium nitrite (387 mg, 5.61 mmol) was added slowly to the solution. The solution was stirred for 2 h while warming from 7 °C to room temperature. The solution was neutralized with 50% ammonium hydroxide in water and extracted with chloroform. The combined chloroform extracts were washed with brine, dried with sodium sulfate, filtered, and evaporated. Flash chromatography over silica gel with 50% hexane in ethyl acetate afforded 43.8 mg (25%) of **8b**. ^{1}H NMR ($CDCl_3$) δ: 8.19 (m, 2H), 7.60 (m, 2H), 7.44 (m, 3H), 7.26 (m, 2H), 7.13 (m, 2H), 4.65 (d, J = 6 Hz, 1H), 4.42 (s, 1H), 2.82 (dd, J = 4.5, 8.7, 1H), 2.40 (br s, 1H), 2.04 (dt, J = 4.5, 11.7, 1H), 1.94 (dd, J = 8.7, 12 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 159.4 (d, J = 237 Hz), 149.3 (d, J = 46.9 Hz), 145.3 (d, J = 14.3 Hz), 140.3, 140.2, 139.7, 139.6, 134.4, 134.3′, 128.9, 128.8, 128.6, 128.5, 128.3, 126.4, 123.2 (d, J = 28.3 Hz), 119.5 (d, J = 27.0 Hz), 67.6, 61.3, 41.9, 37.7. To a stirred, –10 °C solution of the free amine in 2 mL of methylene chloride was added 1 mL of hydrochloric acid in ether (1 M). The solution was stirred for 3 h while warming to 10 °C. The solution was evaporated and dried on the vacuum pump overnight. Recrystallization from chloroform−ether provided 45.2 mg (89.5%) of a white solid. Anal. Calcd ($C_{21}H_{18}ClFN_2 \cdot {}^2/_3H_2O$): C, H, N.

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Supporting Information Available: Results from elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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